Paragraph 4, bridging pages 2 and 3 has been amended as follows:

The group of genes is described in more detail in Figure 1. The expression strength, i.e., the amount of gene product, is determined by at least one of the genes in a patient sample that is mentioned in ~~Figure 1~~ Figures 1a and b and compared to that of a control sample (women without endometriosis). The samples that are to be compared must both originate from the secretory phase, thus from the range of days 15-28 after the last menstruation. A decreased expression strength of at least one of the above-mentioned genes in the patient sample indicates the presence of an endometriosis.

On page 3, the second full paragraph has been amended as follows:

A gene product is either mRNA, the cDNA that is derived therefrom, a polypeptide or portions of a polypeptide. The amino acid sequences of the polypeptides are depicted in ~~Figure 2~~ Figures 2a-m.

Paragraph 4 bridging pages 3 and 4 has been amended as follows:

The gene product polypeptide or a segment of a polypeptide is detected by immunoassay. To this end, specific antibodies are produced using one or more polypeptides that are selected from the group that is described in ~~Figure 2~~ Figures 2a-m. The antibodies can be monoclonal or polyclonal. They can be directed against respectively the entire polypeptide or against fragments

thereof. Such an antibody is obtained according to standard methods by immunization of test animals. The antibodies are then used in, e.g., an ELISA (enzyme-linked-immunosorbent assay), in an RIA (radioimmunoassay) or in the immunohistochemistry for determining the amount of the gene product (Aoki, K. et al. 1996; Forensic Sci. Int. 80, 163-173).

On page 4, the first full paragraph has been amended as follows:

The invention further relates to the use of an antibody chip according to the invention for diagnosis of endometriosis. Antibody chips are miniaturized vehicles, in most cases made of glass or silicon, on whose surface antibodies of known specificity are immobilized in an ordered grid of high density. The detection of the protein/protein interactions can be carried out by mass spectrometry, fluorescence or surface plasmon resonance. Antibodies that specifically bind the proteins that are selected from the group that is described in ~~Figure 2~~ Figures 2a-m can be immobilized on the antibody chip. Methods for the production and use of antibody chips are described in Kreider BL, Med Res Rev 2000, 20:212-215.

On page 5, the second full paragraph has been amended as follows:

The hybridization can also be carried out with the aid of a DNA chip. In addition, the invention therefore relates to a DNA chip, on which at least one oligonucleotide is immobilized, which corresponds to the complete cDNA sequence or a partial sequence or a complementary sequence of a gene that is selected from the group that is described in ~~Figure 1~~ Figures 1a and b. The invention thus further relates to the use of a DNA chip according to the invention for diagnosis of endometriosis.

Paragraph 3 bridging pages 6 and 7 has been amended as follows:

~~Fig. 1 shows~~ Figs. 1a and b show the list of genes that can be adjusted downward in the secretory phase in the presence of an endometriosis and thus can be used for a diagnosis of the endometriosis. Listed in column 1 are the names and the data bank number (accession numbers) of the genes, which were found in analysis to be differentially regulated. In column 2 is found the comparison of samples from the secretory phase (secr. phase), in each case **endometriosis** versus **normal** (no endometriosis); **down** refers to the state of downward adjustment. The first number in parentheses indicates how often the gene was found to be regulated upward, and the second number indicates how often the gene was found to be adjusted downward. For this analysis, 20 individual comparisons were performed. In column 3, the comparison of samples

from the proliferative phase (prol. phase) is found. For this analysis, 30 individual comparisons were performed. The designation **down** describes the same state as in column 1, **nc** means **no correlation** (no correlation), i.e., this gene is found to be regulated both downward and upward. The meaning of the numbers is analogous to column 2. In the fourth column, the comparison of samples from the secretory phase with samples from the proliferative phase is found. Here, the endometrium of women without endometriosis was compared to one another. For this analysis, 25 individual comparisons were performed. The designation up describes the state of the upward regulation. The meaning of the numbers is analogous to column 2.

On page 7, the first full paragraph has been amended as follows:

~~Figure 2 shows~~ Figures 2a-m show a list of polypeptides, which are coded by the genes that are depicted in ~~Figure 1~~ Figures 1a and b and are expressed to a reduced extent in the presence of an endometriosis.

Paragraph 2 bridging pages 10 and 11 has been amended as follows:

The results are depicted in ~~Figure 1~~ Figures 1a and b . The listed genes can be considered as differentiation markers. Assuming that the proliferative phase is dominated by the names according to proliferative processes, the secretory phase is more likely considered as a differentiation phase. Against this

background, genes that are important to the differentiation should be regulated upward during this phase (cf. ~~Figure 1~~ Figures 1a and b, column 4) and regulated downward or regulated to remain at the same level during the proliferative phase (cf. ~~Figure 1~~ Figures 1a and b, column 3). The genes that are listed in column 1 meet these criteria and are therefore referred to as differentiation markers. The fact that these genes are adjusted downward in women with endometriosis (column 2) indicates a disrupted differentiation in the secretory phase.

On page 11, the second full paragraph has been amended as follows:

First, the suitable DNA sequences are determined from the genes that are selected from the group that is described in ~~Figure 1~~ Figures 1a and b. Sequences that can hybridize with the selected gene transcripts are suitable. The oligonucleotides are then produced on the chip by a chemical process that is based on the photolithographic process. To this end, photolithographic masks are used, which were produced by suitable computer algorithms.

On page 11, the third full paragraph has been amended as follows:

The labeled RNA is incubated with the chip in a hybridization furnace. The chip is then analyzed in a scanner, which determines the hybridization profile. As a result, it can be determined whether one or more of the genes of the genes

listed in ~~Figure 1~~ Figures 1a and b is regulated downward in the secretory phase, which indicates an endometriosis.

On page 12, the first full paragraph has been amended as follows:

To perform an immune test, specific antibodies that bind to the polypeptides that are described in ~~Figure 2~~ Figures 2a-m are required. The antibodies can be monoclonal or polyclonal antibodies, which are directed against the purified proteins, peptides, selected from the coded proteins, or recombinantly produced fragments or whole protein.

Listing of Claims:

Claim 1 (Currently Amended) ~~Method~~ A method for in vitro diagnosis of endometriosis in a subject in need thereof, ~~characterized in that~~ comprising:

determining the amount of gene product of at least one gene in an endometrial sample obtained during said subject's uterine secretory phase, wherein said gene is ~~from the group that consists of~~ selected from: fibronectin, insulin-like growth factor binding protein-2, transmembrane receptor PTK7, platelet-derived growth factor receptor alpha, collagen type XVIII alpha 1, subtilisin-like protein (PACE4), laminin M chain (merosin), elastin, collagen type IV alpha 2, p27 interferon alpha-inducible gene, reticulocalbin, aldehyde dehydrogenase 6, gravin, nidogen, and phospholipase C epsilon, and

comparing ~~is determined in a patient sample and is compared to~~ the amount of ~~this~~ said gene product to ~~in~~ a normal endometrial secretory phase control ~~sample~~,

whereby a smaller amount of ~~this~~ said gene product in said subject's sample indicates the presence of an endometriosis.

Claim 2 (Originally Filed) Use of antibodies against one or more proteins coded by genes from the group that consists of fibronectin, insulin-like growth factor binding protein-2, transmembrane receptor PTK7, platelet-derived growth factor receptor alpha, collagen type XVIII alpha 1, subtilisin-like protein (PACE4), laminin M chain (merosin), elastin, collagen type

IV alpha 2, p27 interferon alpha-inducible gene, reticulocalbin, aldehyde dehydrogenase 6, gravin, nidogen and phospholipase C epsilon or against parts of the polypeptide or the proteins for diagnosis of endometriosis.

Claim 3 (Originally Filed) DNA chip, wherein at least one oligonucleotide that comprises a partial sequence of a DNA that is selected from the group that consists of fibronectin, insulin-like growth factor binding protein-2, transmembrane receptor PTK7, platelet-derived growth factor receptor alpha, collagen type XVIII alpha 1, subtilisin-like protein (PACE4), laminin M chain (merosin), elastin, collagen type IV alpha 2, p27 interferon alpha-inducible gene, reticulocalbin, aldehyde dehydrogenase 6, gravin, nidogen and phospholipase C epsilon or their complementary sequences, is bonded to the chip.

Claim 4 (Cancelled)

Claim 5 (Newly Added) A method of claim 1,

wherein said determining is performed on a DNA chip comprising at least one oligonucleotide which corresponds to the complete cDNA sequence, a partial sequence thereof, or a complement thereof, selected from at least one said gene.

Claim 6 (Newly Added) A method claim 1,

wherein said DNA chip comprises at least one cDNA, or oligonucleotide thereof, corresponding to a gene selected from: insulin-like growth factor binding protein-2, transmembrane receptor PTK7, platelet-derived growth factor receptor alpha, collagen type XVIII alpha 1, subtilisin-like protein (PACE4), laminin M chain (merosin), elastin, collagen type IV alpha 2, p27 interferon alpha-inducible gene, reticulocalbin, aldehyde dehydrogenase 6, gravin, nidogen, phospholipase C epsilon, or a complement thereof.

Claim 7 (Newly Added) A method of claim 1,

wherein said determining is performed by polymerase chain reaction or Northern blot.

Claim 8 (Newly Added) A method of claim 1,

wherein said determining is performed on a plurality of said genes.

Claim 9 (Newly Added) A method of claim 1,

wherein said control is obtained from the same subject after therapy to evaluate the course of the disease.

Claim 10 (Newly Added) A method for in vitro diagnosis of endometriosis in a subject in need thereof, comprising:

determining the amount of gene product of at least one gene in sample obtained during said subject's uterine secretory phase, wherein said gene is selected from: insulin-like growth factor binding protein-2, transmembrane receptor PTK7, platelet-derived growth factor receptor alpha, collagen type XVIII alpha 1, subtilisin-like protein (PACE4), laminin M chain (merosin), elastin, collagen type IV alpha 2, p27 interferon alpha-inducible gene, reticulocalbin, aldehyde dehydrogenase 6, gravin, nidogen, and phospholipase C epsilon, and

comparing said amount of said gene product to a normal uterine secretory phase control,

whereby a smaller amount of said gene product in said subject's sample indicates the presence of an endometriosis.

Claim 11 (Newly Added) A method of claim 10,

wherein said determining is performed on a DNA chip comprising at least one oligonucleotide which corresponds to the complete cDNA sequence, a partial sequence thereof, or a complement thereof, selected from at least one said gene.

Claim 12 (Newly Added) A method of claim 10,

wherein said determining is performed by polymerase chain reaction or Northern blot.

Claim 13 (Newly Added) A method of claim 1,

wherein said determining is performed on a plurality of said genes.

Claim 14 (Newly Added) A method of claim 1,

wherein said control is obtained from the same subject after therapy to evaluate the course of the disease.

REMARKS

Support for the amendments to the claims can be found throughout the specification, e.g., Claims 1 and 10, on Page 9, lines 18-22, Page 11, lines 21-24; Claims 5 and 11, on Page 5, lines 8-15, Page 11, Example 2; Claim 7 and 12, Page 4, lines 15-22; Claims 8 and 13, on Page 6, lines 4-6; Claims 9 and 14, Page 3, lines 12-16.

The following comments are numbered in the same order listed in the Office action dated April 22, 2003.

2. The specification and drawings have been amended to comply with 37 §CFR 1.74.

5., 6. Claim 4 has been canceled without prejudice.

8. Claim 1 has been amended to clarify that the smaller amount of gene product is in the subject's sample.

10. Claim 1 is not anticipated by Kauma et al., *Obstet. Gynecol.*, 72:13-18, 1988, as stated in the Office action.

Kauma et al. analyzed the presence and production of fibronectin protein in peritoneal fluids in normal subjects and patients with endometriosis. They found that peritoneal macrophages from

patients with endometriosis produced more fibronectin per 24 hour period than macrophages isolated from normal individuals. See, e.g., Kauma et al., Page 15, Column 1, last paragraph. On the other hand, the fibronectin concentration in the peritoneal fluid of these patients was significantly lower than in the normal group. See, e.g., Kauma et al., Page 16, Column 1.

The results reported by Kauma et al. were not performed in endometrial samples. Moreover, Kauma et al. does not distinguish at what phase their analysis was performed[1]. Compare, e.g., Claim 1, "determining in endometrial sample obtained during said subject's uterine secretory phase." Claim 10 has also been added in which reference to fibronectin has been deleted. Thus, the cited reference does not anticipate or render obvious the claimed inventions.

In that this is a full and complete response to the Office Action of April 22, 2003, Applicant respectfully requests that this application be allowed and passed to issue. If the Examiner for any reason feels that a personal conference with Applicant's Attorneys might expedite prosecution of this application, the Examiner is respectfully requested to telephone the undersigned locally.

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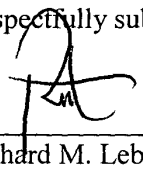
[1] However, on Page 15, Kauma et al. state "There was no significant difference in macrophage fibronectin production between the different clinical stages of endometriosis, although it should be noted that there were relatively small sample numbers for each group of a given stage of endometriosis."

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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RML/jmj